US-PAT-NO: 4828837

DOCUMENT-IDENTIFIER: US 4828837 A

TITLE: Non-crystalline minoxidil composition, its production and application

DATE-ISSUED: May 9, 1989

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uster; Paul S.	Palo Alto	CA	N/A	N/A
Quinn; Yolanda P.	Daly City	CA	N/A	N/A

APPL-NO: 07/032512

DATE FILED: March 30, 1987

US-CL-CURRENT: 424/450, 264/4.1 , 264/4.6 , 424/449 , 424/45 , 428/402.2 , 436/829 , 514/78 , 514/944 , 514/947 , 514/969

ABSTRACT:

An aqueous, noncrystalline minoxidil composition for topical use. The composition contains minoxidil complexed with an amphipathic compound having a pK less than about 5 and containing a single lipophilic chain moiety and a sulfate, sulfonate, phosphate and phosphonate polar moiety. The composition may be formulated in ointment form, in an aqueous vehicle, or dispersed in a fluorochlorocarbon solvent, for spray delivery from a self-propelled spray device.

18 Claims, 20 Drawing figures

Exemplary Claim Number: 1,5,6

Number of Drawing Sheets: 11

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Brief Summary Text - BSTX (5):

The drug itself is a piperidinyl pyrimidine compound which is poorly soluble in **water** and in most **water**-immiscible organic solvents such as chloroform. Heretofore, **minoxidil** has been formulated, for topical use, in an ethanol-based ointment vehicle containing ethanol, propylene **glycol and water**. The solubility of the drug in pure propylene **glycol** is between about 7-9% by weight, and in an ethanol/propylene **glycol/water** vehicle, only about 2%. One drawback of the formulation is the tendency of the **minoxidil** to revert to an insoluble crystalline form when applied to the skin, as the ethanol solvent evaporates. Whether due to the tendency of the drug to crystallize or other factors, the **minoxidil** formulation shows relatively inefficient uptake by the skin. Another limitation is the limited solubility of the drug in the ethanol/propylene **glycol/water** vehicle. Further, evaporation of ethanol, when the formulation is applied to the skin, leaves a viscous propylene **glycol/water** residue which may be objectionable to many users. The drug is poorly soluble in **water** and practically insoluble in lipophilic solvents, such as chloroform. Therefore, predominantly **water**-based or propellant-solvent formulations have not been feasible heretofore.

Brief Summary Text - BSTX (6):

European patent application No. 177,223 discloses a liposomal **minoxidil** composition in which **minoxidil** is present (1) in solution form possibly in a supersaturated state, either encapsulated in lipid vesicles, or in the aqueous or lipid phases of a liposome suspension, and (2) in a finely divided crystalline (solid) form both within and outside the lipid vesicles. Preferred embodiments of the composition are formed by hydrating a **minoxidil** lipid film containing a saturated phosphatidylcholine (PC), such as dipalmitoylphosphatidylcholine (DPPC), cholesterol, and **minoxidil** with an aqueous solution containing **minoxidil** in ethanol/propylene **glycol and water**. **Minoxidil** is present at a final weight concentration of between about 1.2-3%. The composition was found to contain liposomes of various sizes between about 1.mu. to 15.mu., and **minoxidil** crystals. Although the formulation is reported to increase drug uptake by the epidermis when applied topically to skin, it has

the same limitation as the above non-liposomal formulation in that the drug is applied to the skin largely in crystalline form.

Drawing Description Text - DRTX (4):
FIG. 3 is a plot showing changes in minoxidil **solubility,** in a 20% laureth sulfosuccinate mixture, as a function of **pH;**

Drawing Description Text - DRTX (5):
FIG. 4 is a plot showing the increase in minoxidil **solubility** with increased concentrations of laureth sulfosuccinate in a **pH** 5.0 mixture;

Detailed Description Text - DETX (10):
According to an important property of the amphipathic compounds, optimal **solubilization** of minoxidil by the amphipathic compound occurs at a **pH** of about 5 or less, where a significant fraction of the compound exists in free acid form. The **solubility** dependence of minoxidil on **pH** is illustrated in FIG. 3, for a 20% by weight solution of laureth sulfosuccinate (FIG. 2a compound). Between **pH** 7.0 and about 5.0, minoxidil **solubility** increases from about 1.5% to nearly 5%. Little improvement is seen as the **pH** is lowered beyond about 4.5. For most purposes, a **pH** of about 5 is preferred, since good **solubility** is achieved, and skin irritation which may result from below-physiological **pH** is minimized.

Detailed Description Text - DETX (11):
In a preferred method for preparing the composition, a portion of the amphipath is converted to a free acid form, and then "titrated" to the desired **pH,** e.g., **pH** 5.0, with the metal salt form of the compound. This approach is illustrated in Example 1, which describes the preparation of a 20 weight % laureth sulfosuccinate solution having a final **pH** of 5. Here the disodium salt of the compound is converted to the free acid form by passage through a cation exchange resin. Mixing the free acid with the disodium salt, at a ratio of about 1:3, yields a **pH** 5.0 solution suitable for **solubilization** of the minoxidil. It is appreciated that the free acid and salt components effectively buffer the solution at the selected **pH,** obviating the need for additional buffering components.

Detailed Description Text - DETX (13):
Optimal **solubilization** of the minoxidil in an aqueous formulation requires a molar concentration of amphipathic compound to minoxidil of at least about 1:1, and molar ratios of between 1:1 and 1:5 are typical. FIG. 4 illustrates the increasing **solubility** of minoxidil with increasing concentration of amphipath in an aqueous solution at **pH** 5.0. Details are given in Example 4. As seen from the figure, minoxidil **solubility** up to about 5 percent by weight was achieved at the highest amphipath concentration.

Detailed Description Text - DETX (14):
The minoxidil composition is preferably formed by adding dry minoxidil to the aqueous solution of amphipath, prepared as above, to a desired **pH** and amphipath concentration. Typically, the solution is warmed to about 50.degree. C., and the minoxidil is added slowly with stirring. When the minoxidil is completely **dissolved,** the solution is cooled and the **pH** adjusted, if needed. The general method is illustrated in Examples 1 and 2, for the preparation of laureth sulfosuccinate/minoxidil compositions; in Example 5, for the preparation of a Crodafos.TM./minoxidil composition; and in Example 6, for the preparation of a taurocholic acid/minoxidil composition. All of the compositions gave clear aqueous solutions.

Detailed Description Text - DETX (38):
The preparation of the several compositions studies is detailed in Examples 1, 2, and 5-11. The control drug composition used in the studies is a 2% **minoxidil** composition in an ethanol/propylene **glycol/water** vehicle. The transdermal uptake of this control formulation, over a 24 hour period, is shown by the open squares in FIG. 5. The cumulative amount of drug taken accross the skin in the 24 hour period is less than about 1% of the total applied to the skin.

Detailed Description Text - DETX (65):
A 2% dispersion of **solubilized** minoxidil and the free acid of laureth sulfosuccinate was prepared substantially as in Example 1, with the following modifications: The AG50W-X8 column was prepared with 100 g. Two hundred fifty ml of 40% wt/vol disodium laureth sulfosuccinate was diluted to 20% wt/vol surfactant by adding 250 ml distilled water. This solution was passed over the AG50W-X8 cation exchange column and the free acid eluate collector. Four hundred ml of free acid solution was combined with 1,200 ml of 20% disodium laureth sulfosuccinate and 2.0 liters distilled water. The mixture was heated

to 50.degree. C. and 80 grams minoxidil was added slowly with mixing. After minoxidil dissolution, other excipients may be added. The mixture was cooled to room temperature, and the **pH** adjusted to about 5.3.+-.0.1. Distilled water was added to give 4.0 1 of a clear dispersion containing 2% **solubilized** drug and 8% laureth sulfosuccinate.

Detailed Description Text - DETX (67):
Minoxidil **Solubility: pH** Dependence

Detailed Description Text - DETX (68):
A 20% solution of the free acid of laureth sulfosuccinate in distilled water was prepared as described in Example 1A. More acidic solutions of laureth sulfosuccinate were prepared by increasing the proportion of free acid in the free acid/disodium salt mixture, and more basic forms, by decreasing the ratio. The different-**pH** solutions were each heated to about 50.degree. C. and dry minoxidil containing tritiated minoxidil was added slowly with stirring until minoxidil saturation was achieved. The dispersions were cooled overnight at 4.degree. C. and centrifuged. The concentration of minoxidil in the clear solution was determined by scintillation counting. The results, expressed in mg mnoxidil/ml laureth sulfosuccinate solution, are plotted in FIG. 3 for two separate experiments. As seen, minoxidil **solubility** is very low at **pH** 7.0, and increases linearly to a maximum at a **pH** about 4.5-5.0.

Detailed Description Text - DETX (72):
Solutions of the free acid of laureth sulfosuccinate, at concentrations of 0, 5%, 10%, 15%, 20%, and 25% by weight in distilled water were prepared as in Example 1A. Each solution was heated to about 50.degree. C., and radiolabeled minoxidil was added slowly with stirring until minoxidil saturation was achieved, this being monitored as described in Example 3. The **pH** of each solution was adjusted to about **pH** 5 prior to centrifugation and scintillation counting. The results, expressed in mg minoxidil/ml laureth sulfosuccinate solution, are plotted in FIG. 4. Minoxidil **solubility** in the absence of the amphipath is about 3 mg/ml, or 0.3%. With increasing concentrations of the laureth sulfosuccinate, up to 25 weight percent, the **solubility** of minoxidil increases up to about 50 mg/ml, or 5% at **pH** 5.

Detailed Description Text - DETX (106):
The control vehicle was Rogaine.TM. obtained from Upjohn Co. This formulation contains 2% **minoxidil** in an ethanol/propylene **glycol/water** solvent vehicle, and was labeled with tritiated **minoxidil** before testing. One hundred fifty .mu.1 samples were applied to skin patches and the uptake of **minoxidil** across the skin monitored as described. Tyical results for a 24 hour test period are shown in FIG. 5, where the control drug data is indicated by the open squares in the figure. As seen, the rate of uptake of the drug in the control formulation is substantially linear over the test period, and reaches a cumulative maximum, at the end of the test period, of about 30 .mu.g/cm.sup.2, corresponding to about 0.5-1.0% of the total drug applied to the skin.

US-PAT-NO: 5030442

DOCUMENT-IDENTIFIER: US 5030442 A

TITLE: Non-crystalline minoxidil composition

DATE-ISSUED: July 9, 1991

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Uster; Paul S.	Palo Alto	CA	N/A	N/A
Quinn; Yolanda P.	Daly City	CA	N/A	N/A

APPL-NO: 07/333660

DATE FILED: April 4, 1989

PARENT-CASE:

This is a continuation-in-part of U.S. patent application Ser. No. 032,512, filed on Mar. 30, 1987, now U.S. Pat. No. 4,828,837 issued on May 9, 1989.

US-CL-CURRENT: 424/45, 264/4.1 , 424/450 , 428/402.2 , 514/256 , 514/275 , 514/78 , 514/880 , 514/944 , 514/947 , 514/969 , 514/975

ABSTRACT:

An aqueous, noncrystalline minoxidil composition for topical use which has significantly improved flux of the drug through human cadaver skin. The composition contains minoxidil complexed with an amphipathic compound, oleic acid and with pharmaceutically acceptable excipients. The composition may be formulated in an aqueous vehicle, or dispersed in fluorochlorocarbon solvent for spray delivery from a self- propelled spray device.

18 Claims, 24 Drawing figures

Exemplary Claim Number: 1,10

Number of Drawing Sheets: 15

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Brief Summary Text - BSTX (5):

The drug itself is a piperidinyl pirimidine compound which is poorly soluble in **water** and in most **water**-immiscible organic solvents such as chloroform. Heretofore, **minoxidil** has been formulated, for topical use, in an ethanol-based ointment vehicle containing ethanol, propylene **glycol and water**. The solubility of the drug in pure propylene **glycol** is between about 7-9% by weight, and in an ethanol/propylene **glycol/water** vehicle, only about 2%. One drawback of the formulation is the tendency of the **minoxidil** to revert to an insoluble crystalline form when applied to the skin, as the ethanol solvent evaporates. Whether due to the tendency of the drug to crystallize or other factors, the **minoxidil** formulation shows relatively inefficient uptake by the skin. Another limitation is the limited solubility of the drug in the ethanol/propylene **glycol/water** vehicle. Further, evaporation of ethanol, when the formulation is applied to the skin, leaves a viscous propylene **glycol/water** residue which may be objectionable to many users. The drug is poorly soluble in **water** and practically insoluble in lipophilic solvents, such as chloroform. Therefore, predominantly **water**-based or propellant-solvent formulations have not been feasible heretofore and it would be advantageous to have an alternative formulation avoiding the above problems.

Brief Summary Text - BSTX (6):

European patent application No. 177,223 discloses a liposomal **minoxidil** composition in which **minoxidil** is present (1) in solution form possibly in a supersaturated state, either encapsulated in lipid vesicles, or in the aqueous or lipid phases of a liposome suspension, and (2) in a finely divided crystalline (solid) form both within and outside the lipid vesicles. Preferred embodiments of the composition are formed by hydrating a **minoxidil** lipid film containing a saturated phosphatidylcholine (PC), such as dipalmitoylphosphatidylcholine (DPPC), cholesterol, and **minoxidil** in

ethanol/propylene **glycol and water**. **Minoxidil** is present at a final weight concentration of between about 1.2-3%. The composition was found to contain liposomes of various sizes between about 1 .mu. to 15 .mu., and more importantly **minoxidil** crystals. Although the formulation is reported to increase drug uptake by the epidermis when applied topically to skin, it has the same limitation as the above non-liposomal formulation in that the drug is applied to the skin largely in crystalline form.

Drawing Description Text - DRTX (15):
FIG. 3 is a plot showing changes in minoxidil **solubility**, in a 20% laureth sulfosuccinate mixture, as a function of **pH**.

Drawing Description Text - DRTX (16):
FIG. 4 is a plot showing the increase in minoxidil **solubility** with increased concentrations of laureth sulfosuccinate in a **pH** 5.0 mixture.

Detailed Description Text - DETX (8):
According to an important property of the amphipathic compounds, optimal **solubilization** of minoxidil by the amphipathic compound occurs at a **pH** of about 5 or less, where a significant fraction of the compound exists in free acid form. The **solubility** dependence of minoxidil on **pH** is illustrated in FIG. 3, for a 20% by weight solution of laureth sulfosuccinate (FIG. 2a compound). Between **pH** 7.0 and about 5.0, minoxidil **solubility** increases from about 1.5% to nearly 5%. Little improvement is seen as the **pH** is lowered beyond about 4.5. For most purposes, a **pH** of about 5 is preferred, since good **solubility** is achieved, and skin irritation which may result from below-physiological **pH** is minimized.

Detailed Description Text - DETX (9):
In a preferred method for preparing the composition, a portion of the amphipath is converted to a free acid form, and then "titrated" to the desired **pH**, e.g., **pH** 5.0, with metal salt form of the compound. This approach is illustrated in Example 1, which describes the preparation of a 20 weight % laureth sulfosuccinate solution having a final **pH** of 5. Here the disodium salt of the compound is converted to the free acid form by passage through a cation exchange resin. Mixing the free acid with the disodium salt, at a ratio of about 1:3, yields a **pH** 5.0 solution suitable for **solubilization** of the minoxidil. It is appreciated that the free acid and salt components effectively buffer the solution at the selected **pH**, obviating the need for additional buffering components.

Detailed Description Text - DETX (11):
Optimal **solubilization** of the minoxidil in an aqueous formulation requires a molar concentration of amphipathic compound to minoxidil of at least about 1:1, and molar ratios of between 1:1 and 1:5 are typical. FIG. 4 illustrates the increasing **solubility** of minoxidil with increasing concentration of amphipath in an aqueous solution at **pH** 5.0. Details are given in Example 4. As seen from the figure, minoxidil **solubility** up to about 5 percent by weight was achieved at the highest amphipath concentration.

Detailed Description Text - DETX (12):
The minoxidil composition is preferably formed by adding dry minoxidil to the aqueous solution of amphipath, prepared as above, to a desired **pH** and amphipath concentration. Typically, the solution is warmed to about 50.degree. C., or greater and the minoxidil is added slowly with stirring. When the minoxidil is completely **dissolved**, the solution is cooled and the **pH** adjusted, if needed. The general method is illustrated in Examples 1 and 2, for the preparation of laureth sulfosuccinate/minoxidil compositions; in Example 5, for the preparation of a Crodafos.TM./minoxidil composition; and in Example 6, for the preparation of a taurocholic acid/minoxidil composition. All of the compositions gave clear aqueous solutions.

Detailed Description Text - DETX (15):
An alternative way of preparing a composition of this invention is **dissolve** the amphipath (such as Tauranol) with mixing in 15-25% g distilled water or some other aqueous solution such as 0.01% DTPA (w/w) a metal ion chelating agent. Tauranol WS HP (N-methyl cocoyl taurate) in amounts around 0.12 g is added at temperatures between 20.degree.-28.degree. C., preferably at room temperature. The obtained mixture is heated to between 50.degree.-80.degree. C., preferably 70.degree. C., with mixing until mixture clears while maintaining the constant temperature. The mixture is then titrated to **pH** between 1-2 with inorganic acid, preferably with hydrochloric acid. To the resulting solution, 1%, 2% or up to 4% of minoxidil is added slowly with mixing and heating and maintaining the constant temperature in between 60.degree.-8.degree. C., preferably 70.degree. C. until the mixture clears.

Between 1.5 to 3.5, preferably 2.5 g of oleic acid is added slowly, with vigorous mixing at the above temperature, preferably at 70.degree. C. At this point MLVs are formed in the solution with continuing mixing at elevated (70.degree. C.) temperature for about 10-40 minutes, preferably for at least 20 minutes. The solution is cooled to room temperature and aqueous solution is added up to 100 gm. The final **pH** of the solution is between 5.4-6.1.

Detailed Description Text - DETX (37):
The preparation of the several compositions studies is detailed in Examples 1, 2, 5-11 for hairless mouse skin, and example 22 for human cadaver skin. The control drug composition used in the studies is 2% **minoxidil** composition in an ethanol/propylene **glycol/water** vehicle. The transdermal uptake of this control formulation, over a 24 hours period, is shown by the open squares in FIG. 5. The cumulative amount of drug taken across the skin in the 24 hours period is less than about 1% of the total applied to the skin.

Detailed Description Text - DETX (64):
A 2% dispersion of **solubilized** minoxidil and the free acid of laureth sulfosuccinate was prepared substantially as in Example 1, with the following modifications: The AG50W-X8 column was prepared with 10 g. Two hundred fifty ml of 4.0% wt/vol disodium laureth sulfosuccinate was diluted to 20% wt/vol surfactant by adding 250 ml distilled water. This solution was passed over the AG50W-XB cation exchange column and the free acid eluate collector. Four hundred ml of free acid solution was combined with 1,200 ml of 20% disodium laureth sulfosuccinate and 2.0 liters distilled water. The mixture was heated to 50.degree. C. and 80 grams of minoxidil was added slowly with mixing. After minoxidil dissolution, other excipients may be added. The mixture was cooled to room temperature, and the **pH** adjusted to about 5.3.+-.0.1. Distilled water was added to give 4.0 l of a clear dispersion containing 2% **solubilized** drug and 8% laureth sulfosuccinate.

Detailed Description Text - DETX (66):
Minoxidil **Solubility: pH** Dependence

Detailed Description Text - DETX (67):
A 20% solution of the free acid of laureth sulfosuccinate in distilled water was prepared as described in Example 1A. More acidic solutions of laureth sulfosuccinate were prepared by increasing the proportion of free acid in the free acid/disodium salt mixture, and more basic forms by decreasing the ratio. The different-**pH** solutions were each heated to about 50.degree. C. and dry minoxidil containing tritiated minoxidil was added slowly with stirring until minoxidil saturation was achieved. The dispersions were cooled overnight at 4.degree. C. and centrifuged. The concentration of minoxidil in the clear solution was determined by scintillation counting. The results, expressed in mg minoxidil/ml laureth sulfosuccinate solution, are plotted in FIG. 3 for two separate experiments. As seen, minoxidil **solubility** is very low at **pH** 7.0, and increases linearly to a maximum at a **pH** 4.5-5.0.

Detailed Description Text - DETX (70):
Solutions of the free acid of laureth sulfosuccinate, at concentrations of 0.5%, 10%, 15%, 20%, and 25% by weight in distilled water were prepared as in Example 1A. Each solution was heated to about 50.degree. C. and radiolabeled minoxidil was added slowly with stirring until minoxidil saturation was achieved, this being monitored as described in Example 3. The **pH** of each solution was adjusted to about **pH** 5 prior to centrifugation and scintillation counting. The results, expressed in mg minoxidil/ml laureth sulfosuccinate solution, are plotted in FIG. 4. Minoxidil **solubility** in the absence of the amphipath is about 3 mg/ml, or 0.3%. With increasing concentrations of the laureth sulfosuccinate up to 25 weight percent, the **solubility** of minoxidil increases up to about 50 mg/ml, or 5% at **pH** 5.

Detailed Description Text - DETX (102):
The control vehicle was Rogaine.RTM., obtained from Upjohn Co. This formation contains 2% **minoxidil** in an ethanol/propylene **glycol/water** solvent vehicle, and was labeled with tritiated **minoxidil** before testing. One hundred fifty ul samples were applied to skin patches and the uptake of **minoxidil** across the skin monitored as described. Typical results for a 24 hour test period are shown in FIG. 5, where the control drug data is indicated by the open squares in the figure. As seen, the rate of uptake of the drug in the control formulation is substantially linear over the test period, and reaches a cumulative maximum, at the end of the test period, of about 30 ug/cm.sup.2, corresponding to about 0.5-1.0% of the total drug applied to the skin.